UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,288	05/15/2006	Xianghui Yi	34569-716.831	7077

21971 7590 05/12/2009
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
05/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,288	YI, XIANGHUI	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-12,14-19 and 22-29* is/are pending in the application.

4a) Of the above claim(s) *7-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6, 11-12 and 15-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/10/2008 and 09/19/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 4-12, 14-19 and 22-29 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on January 20th 2009 is acknowledged. Claims4-6, 14-19 and 22-25 are amended, claims 27-29 are newly added and claims 13 and 20-21 were cancelled. Claims 7-10 are withdrawn from consideration as being drawn to a non-elected invention. Claims under consideration in the instant office action are claims 4-6, 11-12 and 15-29

Applicants' arguments, filed 01/20/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. All the foreign documents referenced in the IDS's submitted on 07/10/2008 and 09/19/2007 has now been fully considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "BHT" and "BHA" are unclear because there is no

clear definition as to what BHT or BHA stands for. The first recitation of an abbreviation in the claims should be preceded by the full meaning of the abbreviated term so as to clearly convey what the abbreviation means.

Claim Rejections - 35 USC § 103

This rejection is necessitated by the newly submitted claims filed on 01/20/2009.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

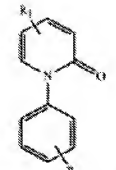
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 4-6 and 11-12 and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolin (US 5716632) in view of Gadekar (US 3839346) and Ansel et al (Pharmaceutical dosage forms and drug delivery systems, Seventh edition, pages 87-92, Copyright 1999)

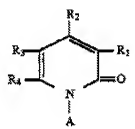
Instant claim 4-6 and 11-25 is drawn towards a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of the compound of formula 1



Formula (I)

Where R1 is methyl at position 5 and R2 is hydroxy at position 4 (instant claims 11 and 12).

Margolin teaches drugs having pharmacological properties which are useful in the mediciinal therapy of fibrotic disease, such drugs including as active ingredients one or more N-substituted 2-(1H) pyridone(s) and/or N-substituted 3-(1H) pyridones as active anti-fibrotic ingredients (abstract, col.1,lines 19-25). Margolin teaches that the use of pirfenidone (5-methyl-1phenyl-2(1H)pyridine) in the reparation and prevention of fibrotic lesions.(col.1,lines 49-53). Margolin teaches N-substituted 3-(1H) pyridones useful in his inventions and exemplifies compounds of formula (col. 11, line 20-33)



where: R2 or R3=alkyl group or hydrogen. as above; A is phenyl, thienyl, etc., or other aryl. R1 and R4 are hydrogen.
Examples of the 2 and 3 pyridones include:
5-Methyl-1-(3-nitrophenyl-2)-(1H) pyridone
5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone

The only difference between the instantly claimed compound and the 5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone taught by Margolin is the substitution in the phenyl ring attached to the pyridone moiety, Instead of the methoxy substituent at position 4 of the phenyl ring taught by Margolin, instant application recites an hydroxy substitution. It has been determined by the court **that hydrogen and methyl are deemed obvious variants**, *In-re Wood* 199 USPQ 137. Accordingly, it would have been obvious for one of ordinary skill in the art to substitute hydrogen for the methyl group of the methoxy function attached at the 4' position of the phenyl group in the compound taught above to obtain a hydroxy derivative.

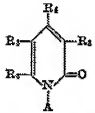
Additionally Margolin teaches examples of medical preparations of the compound pirfenidone useful in his preparations which include (1) capsules (2) tablets (3) powders (4) granules (5) syrups (6) injections (intravenous, intramuscular or drip administration. (7) cream (8) ointment (9) inhalation (10) eye drop (11) suppositories (12) pills, etc. and indicates that the preparations preferred among these are the capsules, injections cream and ointments (col.10, lines 36-45). Margolin teaches capsules comprising 800 mg, 1600 mg or 1600 mg of pirfenidone (col. 10, line 49-50) and hydrophilic ointment containing 5-10% pirfenidone (col. 10, line 54). Margolin additionally teaches that the average oral dosage of pirfenidone for anti-fibrotic activity in humans is 3600 mg/day with a range of from about 2400 mg to about 4800 mg/day and that the administration

may be in divided dosage, for example 1200 milligrams three times per day. (col. 10, lines 56-60). Margolin teaches the effective dosages and rates of application of the compositions of his invention comprising other N-substituted 3 (1H) pyridones to be effective in the range from about one quarter to about twice the dosages given above for pirfenidone (col. 12, lines 20-24) and the composition being administered to a patient at rate of from about 5 mg/kg of body weight per day to about 300 mg/kg of body weight per day(col.12, claim 1). Additionally Margolin teaches that compositions of his invention may be administered in forms consisting of capsules, tablets, powders, granules, syrups, injectable fluids, pills, cream, ointment, inhalable fluids, eye drops and suppositories (col. 12, lines 25-28, claim 9, 12). Margolin, Accordingly, Margolin provides one of ordinary skill in the art motivation to synthesize N-substituted pyridones with different substitution on the phenyl group and formulate a pharmaceutical composition comprising those derivatives.

What Margolin does not teach does the composition comprise one are more pharmaceutically acceptable carriers or excipients.

This deficiency is taught by Gadekar and Ansel et al

Gadekar teaches Novel analgesic compositions containing as the active ingredient the 4 compound 5-methyl-1-phenyl-2(1-H) pyridone (abstract). Gadekar also describes methods of making related pyridones having the formula



II

wherein A is an aromatic group; R_3, R_4, R_5 and R_6 are individually each hydrogen, alkyl, aryl or substituted aryl;

(col. 3, lines 14-27) and in example 3 Gadekar teaches the synthesis of 5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone taught by Margolin above (col.5, lines 69-75).

Gadekar teaches pharmaceutical composition of 5-methyl-1-phenyl-2(1-H)pyridone formulated together with a pharmaceutically acceptable carrier, solid carrier, diluent or a gaseous carrier to provide pharmaceutical compositions in forms suitable for therapeutic administration (col.2, lines 42-49). Gadekar teaches that the solid carriers are useful in formulation of dosage forms such as pills, tablets , powders or cachets for immediate or sustained release and may include flavors or therapeutic adjutants , the liquid carrier can provide flavorful vehicle for oral administration or may be adjusted to tonicity to be used in injectable preparations.(col.2, lines 50-60). Additionally, Gadekar teaches that the standard pharmaceutically acceptable carriers normally used in such pharmaceutical formulations can be utilized in formulating the aforementioned compositions of his invention (col.3, lines 9-13) and in example 30 provides a formulation comprising talc and corn starch as carriers, along with other excipients (col.8, lines 16-31). Accordingly Gadekar provide one of ordinary skill in the art motivation to formulate compositions of N-substituted pyridine derivatives with different types of carriers based on the final dosage form of the formulation.

Ansel et al teaches different types of excipients or pharmaceutical ingredients required to prepare a drug substance into a final dosage form. Ansel teaches the use of solvents to dissolve the drug substance, flavorants to make the product more palatable, colorants to enhance product appeal, preservative to prevent microbial growth and stabilizers such as antioxidants to prevent drug decomposition, diluents or fillers to increase the bulk of the formulation, binders to cause the adhesion of the powdered drug, lubricants to assist smooth tabletting process, disintegrating agents to promote tablet break up after administration and coatings to improve stability. Ansel Et al teaches that for each dosage form the pharmaceutic ingredient establish the primary features of the product and contribute to the physical form, texture, stability, taste and overall appearance (page 87 right col. 3rd paragraph). In Table 3.3 (pages 88-91) Ansel et al. exemplifies several components used for each of the category above. for example Ansel et al. teaches ascorbic acid, butylated hydroxyanisole (BHA) and butylated hydroxytoluene(BHT) as antioxidants (page 88), Mineral oil, alcohol, purified water, sterile water, corn oil, peanut oil etc as examples to be used as solvents (page 90)., starch, Lactose, dibasic calcium phosphate, microcrystalline cellulose as diluents (page 90). Accordingly, Ansel et al provides one of ordinary skill in the art motivation to formulate compositions of drugs using one or more of the listed excipients.

Accordingly Gadekar and Ansel et al. provides motivation to one of ordinary skill in the art to prepare compositions of compounds structurally similar to pirfenidone using different pharmaceutical excipients.

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. It would have been *prima facie* obvious to the skilled artisan to combine the teachings Margolin, Gadekar and Ansel et al. to prepare 5-methyl-1-phenyl-2(IH) pyridine with different substituents at the 4' position of the phenyl moiety. A compound with no phenyl substitution (5-methyl-1-phenyl-2(1-H or pirfenidone) and the one with methoxy substituent on position 4' of the phenyl ring (5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridine) are already taught in the art and pharmaceutical compositions of these compounds and the fact that they possess anti-fibrotic activity has already been taught. Formulation of drugs into tablets or other dosage forms by combining different excipients imparting different functions to the dosage form is well known in the art as taught by Ansel et al. Accordingly, In view of the close structural similarity between the claimed compound in the instant pharmaceutical composition and the compound taught by both Margolin and Gadekar, one of ordinary skilled in the art would have been motivated to formulate instantly claimed compositions, in the expectation that the composition would possess similar anti-fibrotic activity.

An ordinarily skilled artisan will be able to develop such a dosage form with a reasonable expectation of success based on the state of the art at the time of invention in order to provide a better range of anti-fibrotic compounds for treatment of fibrosis.

Response to applicant's arguments filed on 02/27/2009:

In light of the new grounds of rejection above, the arguments submitted on 02/27/2009 which was for the previously submitted rejection is moot. However, with reference to the current rejection examiner responds to the applicant's arguments as follows:

Applicant traverses the above rejection with the following arguments:
(a) The prior art as a whole teaches away from a composition of 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone since during prosecution of European patent # 0702551 the official document submitted by Margolin has data that 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone had a relative anti-fibrotic activity of 0.0 that is no anti-fibrotic activity at all.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive. Examiner would first like to point out that instant claims are drawn towards pharmaceutical compositions and not towards the method of treatment of fibrosis. As such the official document of Margolin actually teaches a pharmaceutical composition of the instantly claimed drug and motivates an ordinarily skilled artisan to further test that composition. Additionally, there are several methods to assay for anti-fibrotic activity and the fact that the instantly claimed drug does not demonstrate any activity in that particular assay tested by Margolin, **will not teach** away an ordinarily skilled artisan from the use of that compound. In fact, a person skilled in the art would have further been motivated to test that particular compound in other available tests for anti-fibrotic activity and in other fibrosis animal models, since

Margolin did in fact demonstrate change in activity of structurally modified compounds similar to the instantly claimed compounds.

Additionally, examiner believes that the prior art used in the rejection above would still be enough motivation for an ordinarily skilled artisan to develop pharmaceutical compositions as instantly claimed since the art used here are immediately accessible to the artisan. An ordinarily skilled artisan would be motivated to develop compositions of the compound and test them for anti-fibrotic activity with a reasonable expectation of success based on the teachings of the references used in this rejection.

Conclusion

Claims 4-6 and 11-12 and 21-29 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614